REMARKS/ARGUMENTS

Claims 11-13, 15-22, and 24-28 are active in this application. Support for the amendments to Claims 11 and 20 is found in Claims 14 and 23 and the specification as originally filed. No new matter is added by these amendments. Favorable reconsideration is requested.

The present invention provides a method for intranasally administering a composition comprising a microparticle having a protein and an antibody specific for the protein adsorbed thereon, wherein said administering comprises contacting a microparticle having a protein and an antibody thereon with the nasal mucosa of a patient in need thereof. This method provides an efficient means of presenting the microparticles to a patient and yield significantly better results than the methods previously employed. For example, on page 4, line 4 of the specification, this method provides 400,000 times higher levels than administration in the intestine.

The rejection of Claims 11-28 under 35 U.S.C. § 103(a) over Smith et al and Almeida et al is respectfully traversed.

Smith is described in the present specification on page 2, last paragraph. Smith describes a pharmaceutical for oral administration, i.e., absorbed in the intestine, in which the pharmaceutical has a protein and an antibody absorbed on a microparticle. Smith does not describe intranasal administration. For intranasal administration, the Examiner relies on Almeida for nasal delivery and alleges that one would employ the Smith pharmaceutical intranasally based on the advantages of nasal delivery (page 6 of the Office Action).

Applicants respectfully disagree and submit that the combined teachings of the cited references do not suggest the present method of intranasal administration and as such fail to support a *prima facie* case of obviousness. In particular, the alleged support for intranasal

administration in Almeida does not, in fact, suggest that nasal administration is better than oral administration, i.e., intestinal delivery. Applicants direct the Examiner's attention to Almeida on page 471, second column, second paragraph:

> The mode of entry of nasally administered particles into the circulation is not fully understood and few investigators have postulated putative mechanisms (Kuper et al., 1992). The nasal adsorption of fluorescent polystyrene particles has been observed, which suggests that the mechanism of solid particle uptake by the nasal mucosa is **similar** to that found in the gut (Alpar et al., 1994).

Assuming for arguments sake that a *prima facie* case of obviousness had been made, t even a *prima facie* case is rebutted by Applicants showing already of record where greater than 400,000 times more microparticles are absorbed in the nasal mucosa compared to the intestines (MPEP § 716.02(a) "GREATER THAN EXPECTED RESULTS ARE EVIDENCE OF NONOBVIOUSNESS"). For the Examiner's convenience a discussion of the results presented on pages 3, 4 and 11 of the present specification are presented below:

(1) In the intestine: yield/cm^2 = 4.4 x 10^{-9} (=0.0000044°/oo) - page 3, line 28

(2) In the nasal mucosa: yield/cm^2 = 1.7 x 10^{-3} (=1.7°/oo) which is 400,000 times greater than the absorption in the intestine - page 11, lines 22-28.

Thus, it is submitted that nothing in the combined teachings of the cited references suggest nor could have predicted the 400,000 times greater absorption of the microparticle composition in the nasal mucosa compared to the intestines.

In the parent application, the Office questioned the comparisons provided in the specification because the experiments presented for the intestine were performed *in vivo* at 37°C and the experiments performed for the nasal mucosa were performed *in vitro* at 27°C. Applicants submit that the data are comparable and provide the following to help the Examiner understand this point.

As discussed on page 9, lines 25 to 27: "The incubation temperature was 27°C ± 1°C. As compared with 37°C, this temperature lowers metabolism and transport twice as much, but renders the isolated tissue more stable." Since microparticle transport at 27°C is 400,000 times greater than transport in the intestine at 37°C (page 11, lines 22-28), it would be expected that if the experiments in the nasal mucosa were performed at 37°C the resulting increase through the nasal mucosa would have been approximately 800,000 times greater than the intestine. Clearly, this result is even more dramatic and is greater than an expected result (MPEP § 716.02(a)). Additionally, Applicants note that since the nasal mucosa (nostril) is exposed and not as well insulated by the body (compared to an internal organ such as the intestine), the temperature of the nasal mucosa is more susceptible to changes in the ambient temperature. For example, if the ambient temperature is approximately 22°C, the temperature of the nostril would be approximately 32°C and as the ambient temperature declines, the nostril temperature will also decline. Thus, the experimental conditions of 27°C more closely mimics the real temperature of the nasal mucosa in a living individual.

Turning to the issue comparing *in vitro* testing and *in vivo* testing, Applicants submit that the comparison of *in vivo* intestinal data and *in vitro* nasal mucosa data is appropriate. Intestinal tissue isolated for *in vitro* testing consists of mono-layered epithelium, a layer of connective tissue underneath (which contains the ducts and thick lymphoid tissue of the Peyer's patches), two layers of musculature, another layer of connective tissue and a serous membrane. *In vivo* the proteins are adsorbed by intestinal epithelium, then pass into connective tissue where they then reach the ducts and where the microparticle numbers are measured (see page 3, lines 20-23). Contrast this adsorption pathway to the adsorption *in vitro*, where the proteins have to pass through the whole wall of the isolated intestine before being measured and thus much of the proteins to be measured are lost. Accordingly, the absorption of proteins in the intestine is significantly more efficient *in vivo* than *in vitro*. The

nasal mucosa membranes isolated for *in vitro* testing consists of a psuedoepithelium layer and a thin layer of connective tissue. Thus, the adsorbed protein passes through the nasal mucosa in much the same way both *in vitro* and *in vivo*, *in vivo* the protein reaches the ducts whereas *in vitro* the protein passes through the thin layer connective tissue.

Accordingly, comparing transport in the nasal mucosa *in vitro* at 27°C with the transport in the intestine *in vivo* at 37°C is physiologically more correct than comparing transport of the two tissues both *in vitro* or *in vivo* at the same temperature. It is submitted in view of the foregoing that the instant claims are not obvious in view of the combined teachings of the cited references since the references fail to suggest neither the present method nor the highly significant absorption of the microparticle composition in the nasal mucosa when compared to the absorption of the same microparticle composition in the intestine. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 11-13, 15-22 and 24-28 under 35 U.S.C. § 112, first paragraph is traversed.

As stated by the Office, the specification enables the claim where the antibody is specific for the protein (page 2 of the Official Action). Claims 11 and 20 have been amended to include this definition from Claims 14 and 23, respectively. Accordingly, withdrawal of this ground of rejection is requested.

In the event the Examiner requires clarification or wishes to discuss any of the foregoing information, he is invited to contact the undersigned to resolve the matter expediently.

Applicants submit that the present application is now in condition for allowance.

Early notification of such is earnestly solicited.

Respectfully submitted,

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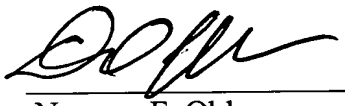

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